REMARKS/ARGUMENTS

All claim amendments are made without prejudice and do not represent an acquiescence in any ground of rejection. Reconsideration of the captioned application based on the previous amendments and following remarks is respectfully requested.

Applicants respectfully thank the Examiner for the interview conducted on December 22, 2005. With regard to the Interview Summary dated December 29, 2005, Applicants agree to the Examiner's review but do respectfully point out that the originally filed application supports the observed results beyond the physiological concentration of ATP, such as from about 1.5 mM to about 6.5 mM ATP, in Table 2 on page 26.

STATUS OF THE CLAIMS

Claims 1 - 9, 20 - 23 are under examination. After entry of this amendment, claims 1-9, 20 - 26 will be pending and under consideration.

Claims 1, 9, 20, 21, and 23 have been amended to more particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Applicants submit that the amendments are fully supported by the specification as filed, and no new matter is being added. For example, the physiological concentrations of ATP and pyrophosphate have been described in the originally filed application, at line 7 on page 27 and at line 8 on page 31. The recited particular concentrations of ATP in the range of from about 1.5 mM to about 6.0 mM and the recited particular concentration of pyrophosphate at about 150 μM have been described, as one example, in Table 2 on page 26.

Applicants further submit new Claims 24 - 26, which are being added to present claims of varying scope. Supports for new Claims 24 - 26 are found in the application as originally filed.

PRIOR ART References

In the Office Action dated Oct. 12, 2005, the Examiner considered two pieces of prior art to be allegedly germane to Applicant's disclosure: the Shafer paper (1998, *Ann. Intern. Med.* 128(11): 906-11) and the Winters paper (1998, J. Clin. Invest. 102(10): 1769-1775). The Examiner noted "both references disclose HIV-1 AZT resistant mutants carrying M41L/M184V/T215Y mutations."

The current invention claims an in vitro enzymatic assay method for determining the AZT susceptibility of a HIV RT enzyme. Such an in vitro enzymatic assay method is applicable to any HIV RT enzyme, not limited to any particular mutant. Neither of the two references provides description on the in vitro enzymatic assay methods for determining AZT susceptibility of a HIV RT enzyme. The teaching of the references neither anticipates the present invention nor renders the present invention obvious. Therefore, Applicants respectfully assert that Applicants fail to see the references to be germane to the present invention and respectfully traverse such a conclusion from the Examiner.

REJECTIONS UNDER 35 U.S.C. §103(a)

In the Office Action dated Oct. 12, 2005, the Examiner rejected claims from the present invention under 35 U.S.C. §103(a). By combining ATP or PPi at an appropriate concentration with a detectable dNTP substrate, Applicants have obtained an unexpected result, an in vitro AZT-resistance assay that detected the level of AZT-resistance which is reasonably correlated to the result obtained from the viral phenotypic assay, see for example, Paragraph 1 on Page 30 of the originally filed application. Therefore, Applicants respectfully request that the Examiner withdraw the rejection under 35 USC § 103(a).

Obviousness under 35 U.S.C. §103(a) is a question of law based on the following factual inquiries: 1) the scope and the content of the prior art; 2) the differences between the prior art and the claims at issue; 3) the level of ordinary skill in the art; and 4) objective evidence of secondary considerations. Graham v. John Deere Co., 383 U.S. 1, 17, 148 U.S.P.Q. 459, 567 (1966).

The fact that a patent specifically discloses and claims a combination of features previously used in two separate devices (or methods) is not fatal to patentability. A basic issue is whether applied references, alone or in any combination, suggest the claimed invention as a solution to the specific problem solved. The claimed invention achieved new and unexpected results nowhere suggested in the prior art, and that achievement was overlooked. It is erroneous to focus the inquiry "solely on the product [or methods] created, rather than on the obviousness or non-obviousness of its creation." The initial inquiry should be directed to the vintage point of attacking the problem solved by the invention at the time the invention was made. When prior art itself does not suggest or render obvious the claimed solution to that problem, the art involved does not satisfy the criteria of 35 U.S.C. §103(a) for precluding patentability. Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452 (Fed. Cir. 1984).

The present invention achieved new and unexpected results nowhere suggested in the prior art. At the time the invention was made, there lacked an in vitro HIV RT enzymatic assay that could sensitively detect AZT resistance, see for example pages 5 – 7 of the originally filed specification. While high resistance to AZT (in some mutants over a 100-fold increase in IC_{50} value) had been measured from the viral phenotypic assays, most in vitro RT enzymatic assays demonstrated little or no correlation to the level of resistance observed with the viral phenotypic assays (see also Lennerstrand et al., 2001, *J. of Virology* 75:7202-7205). Although an increase in AZT resistance of up to 5-fold was demonstrated by Arion et al. (1998, *Biochemistry* 37:15908-17) and Meyer et al. (1999, *Mol. Cell* 4:35-43) with a mutant HIV-1 RT (D67N/K70R/T215F/K219Q) in an in vitro HIV RT enzymatic assay involving 0.5 mM pyrophosphate (PPi) and 3.2 mM ATP, respectively, the increase does not correlate to the 100-fold increase in IC_{50} for AZT measured from the viral phenotypic assay (Larder and Kemp, 1989, *Science* 246:1155–1158, Table 2). Applicants discovered, for the first time, that adding ATP or PPi at an appropriate concentration to an in vitro HIV RT enzymatic assay involving a detectable dNTP substrate resulted in more sensitive detection of AZT resistance as compared with the prior art in vitro assays. As shown in Table 3 on page 29 of the originally filed

application, the AZT resistance detected from an in vitro HIV RT enzymatic assay of the invention reasonably correlated to the in vivo data measured from the viral phenotypic assay.

Meyer et al. (1999) in view of Ekstrand et al. (1996) does not render the present invention obvious under 35 U.S.C. §103(a), because neither of the two references suggested to combine ATP with the RT assay of Ekstrand et al. (that employs BrdUTP as a detectable dNTP) to achieve a more sensitive detection of AZT resistance. At most, the teaching in Meyer et al. might motivate a skilled artisan to try to add ATP to the RT assay of Ekstrand et al. However, obvious to try is an improper basis for a § 103(a) rejection when there is no suggestion or expressed expectation of success in the prior art that would have led one to perform the experimentation in the first place. Although obviousness does not require absolute predictability, a reasonable expectation of success is necessary. In re TomlinsonHall and Geigle, 363 F.2d 928 (C.C.P.A. 1966); In re Clinton, 527 F.2d 1226 (C.C.P.A. 1976).

Applicant(s) urges that in the instant case, there was no reasonable expectation of success that adding ATP to the RT assay of Ekstrand et al. would yield significantly better detection of AZT resistance than that of Meyer et al. Note that the detection of AZT resistance of a mutant RT enzyme is more than the mere detection of the activity of the mutant RT enzyme. The AZT resistance of a mutant RT enzyme is determined by measuring both the activity of the mutant RT enzyme and the activity of a wild-type RT enzyme in the presence of AZT, and then comparing the measured activity of the mutant RT enzyme with that of the wild-type. Even if we assume, arguendo, the RT assay of Ekstrand et al. is more sensitive in measuring RT activity than that which was used by Meyers et al., the RT assay of Ekstrand et al. would have detected increased activities from both the mutant RT enzyme and the WT RT enzyme. Because the AZT resistance is obtained by comparing the measured activity of the mutant RT enzyme with that of the wild-type, increased activities in both the mutant and the wild-type RT enzymes would not necessarily result in increased AZT resistance. Thus, it is unexpected that adding ATP to the RT assay of Ekstrand et al. would result in

significant better detection of AZT resistance than that of the prior art – a new and unexpected result Applicants have discovered only by actually adding ATP to the RT assay of Ekstrand et al. and carrying out the requisite steps. Hence, it may be obvious to try, but such is not the standard under which obviousness established because a reasonable expectation of success is not present in this case.

Methods of the present invention provide a solution to the specific problem of correlating results from an in vitro enzymatic assay with those from a viral phenotypic assay for a wide range of mutant HIV RT enzymes. Such a solution is neither described nor suggested by Meyer et al (1999) or Ekstrand et al (1996). "It is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to [use] that which the inventor taught against its teacher."" (Quoting W.L. Gore v. Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983)). In re Lee, 61 U.S.P.Q.2d at 1434 (Fed. Cir. 2002).

For the reasons detailed above, Applicants respectfully request that the Examiner withdraw the rejection under 35 USC § 103(a) over Meyer et al (1999) in view of Ekstrand et al (1996). For similar reasons, Applicants respectfully request that the Examiner withdraw all the other rejections under 35 USC § 103(a), such as that over Arion et al (1998) in view of Ekstrand et al (1996), that over Meyer et al. (1999) in view of Ueno et al. (1995), or that over Arion et al. (1998) in view of Ueno et al. (1995).

CONCLUSION

Entry of the foregoing amendment is respectfully requested because the amendment is believed to place the application in condition for allowance.

Applicants respectfully traverse the Examiner's conclusion that the references of Shafer (1998) and Winters (1998) are germane to the present invention, because the current invention relates to an in vitro enzymatic assay method applicable to any HIV RT enzyme, not relying on any particular mutant as that described in the references, and that the teaching of the references neither anticipates the present invention nor renders the present invention obvious. Applicants respectfully request that the Examiner

withdraw all rejections under 35 USC § 103(a) because methods of the present invention achieved new and unexpected results over what would be predicted by merely combining the references - an in vitro AZT-resistance assay that detected the level of AZT-resistance which is reasonably correlated to the results obtained from the viral phenotypic assays.

In view of the foregoing amendments and remarks, Applicants submit that the application is in condition for allowance, and respectfully request that a timely Notice of Allowance be issued in this case.

Should the Examiner have any questions or concerns regarding the present response, he is invited to contact the undersigned at the telephone number provided below.

Respectfully Submitted,

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